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EPIDEMIOLOGY

No evidence for glutathione S-transferases *GSTA2*, *GSTM2*, *GSTO1*, *GSTO2*, and *GSTZ1* in breast cancer risk

Irena E. Andonova · Christina Justenhoven · Stefan Winter · Ute Hamann · Christian Baisch · Sylvia Rabstein · Anne Spickenheuer · Volker Harth · Beate Pesch · Thomas Brüning · Yon-Dschun Ko · Varban Ganev · Hiltrud Brauch

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Abstract Breast cancer is a complex disease and in recent years a number of breast cancer susceptibility genes have been identified, but the role of low penetrance susceptibility genes has not been completely resolved. Glutathione S-transferases (GSTs) are phase II xenobiotic metabolizing enzymes involved in the detoxification of chemical carcinogens and environmental pollutants and play an important role in cell defense mechanisms against oxidative stress. They have been in the spot light for the investigation of a potential association with breast cancer risk but so far, sparse or even no data for a potential contribution of *GSTA2*, *GSTM2*, *GSTO*, and *GSTZ* to breast cancer risk are available. We genotyped *GSTA2*_448_C > G (rs2180314), *GSTA2*_742_A > C (rs6577), *GSTM2*_-832_T > C (rs638820), *GSTO1*_-1242_G > A (rs2164624), *GSTO1*_419_A > C (rs4925), *GSTO2*_-183_A > G (rs2297235), *GSTO2*_342_A > G (rs156697), *GSTZ1*_-4378_A > G (rs1046428), and *GSTZ1*_94_G > A (rs3177427) by MALDI-TOF MS in the German GENICA breast cancer case–control collection of 1021 cases and 1015 controls and performed breast cancer risk association in general and with respect to the stratifications: menopausal status, family history of breast or ovarian cancer, use of oral contraceptives, use of hormone therapy, body mass index, and smoking as well as histopathological tumor characteristics including hormone receptor status, grade, histology, and node status. We did not observe any breast cancer risk associations and conclude that it is unlikely that glutathione S-transferases GSTA2, GSTM2, GSTO1, GSTO2, and GSTZ1 participate in breast cancer susceptibility.

Keywords GSTs · Polymorphisms · Breast cancer risk

Introduction

A number of breast cancer susceptibility genes have been identified in recent years either via whole genome or candidate gene approaches [1, 2], but the role of low penetrance susceptibility genes has not been completely

I. E. Andonova · C. Justenhoven · S. Winter · H. Brauch (✉)
Dr. Margarte Fischer-Bosch Institute of Clinical Pharmacology, 70376 Stuttgart, Germany
e-mail: hiltrud.brauch@ikp-stuttgart.de

I. E. Andonova · C. Justenhoven · S. Winter · H. Brauch
University of Tübingen, Tübingen, Germany

I. E. Andonova
Department of Medical Chemistry and Biochemistry, Institute of Experimental Pathology and Parasitology, Bulgarian Academy of Science and Medical University, Sofia, Bulgaria

U. Hamann
Molecular Genetics of Breast Cancer, German Cancer Research Center (DKFZ), Heidelberg, Germany

C. Baisch · Y.-D. Ko
Department of Internal Medicine, Evangelische Kliniken Bonn gGmbH, Johanniter Krankenhaus, Bonn, Germany

S. Rabstein · A. Spickenheuer · V. Harth · B. Pesch · T. Brüning
BGFA-Research Institute of Occupational Medicine of the German Social Accident Insurance, Ruhr University of Bochum, Bochum, Germany

V. Ganev
Faculty of Medicine, Sofia University St. Kliment Ohridski, Sofia, Bulgaria

resolved. Because breast cancer is a multifactorial complex disease resulting from endogenous and exogenous exposures, glutathione S-transferases (GSTs) are in the spot light for the investigation of a potential association with breast cancer risk. GSTs are a family of phase II detoxifying enzymes that catalyze the conjugation of glutathione to a wide variety of electrophilic compounds. Besides detoxifying electrophilic xenobiotics such as chemical carcinogens, environmental pollutants, and antitumor agents, these transferases inactivate endogenous alpha, beta-unsaturated aldehydes, quinones (e.g., catechol estrogen quinones known to be genotoxic procarcinogens), epoxides, and hydroperoxides formed as secondary metabolites during oxidative stress [3, 4]. Altogether, they facilitate the clearance of endogenous hydrophobic compounds including hormones, steroids, haem, bilirubin, and bile acids and are essential for the metabolism of environmental carcinogens, drugs, and pesticides by catalyzing the conjunction of reactive chemical intermediates to water soluble glutathione conjugates [5]. They are also intimately involved in the biosynthesis of leukotrienes, prostaglandins, testosterone, and progesterone, as well as the degradation of tyrosine [6].

Based on amino acid similarities, seven classes of cytosolic GSTs are recognized in mammalian species designated Alpha (GSTA), Mu (GSTM), Pi (GSTP), Sigma (GSTS), Theta (GSTT), Omega (GSTO), and Zeta (GSTZ). They consist of multiple isoforms and have broadly cytoprotective function. In humans, all seven classes exhibit genetic polymorphisms of which 35 common *GST* alleles and their effect on the respective protein have been reviewed [6]. Because *GST* genetic/functional variations are suspect to increase the susceptibility to carcinogenesis including the risk to develop breast cancer, *GST* polymorphisms have been subject to numerous breast cancer association studies with a focus on the frequent *GSTM1* and *GSTT1* deletion (loss of function) as well as *GSTP1* non-synonymous single nucleotide (reduction of substrate binding capacity) polymorphisms. Results from a meta analysis of 19 studies indicated no relationship of the common *GSTM1* null variant with breast cancer risk [7], however, a study based on the distinction between *GSTM1* +/+ and −/− genotypes found an association between breast cancer risk and the *GSTM1* +/+ genotype [8]. Similarly, no breast cancer risk association was observed for *GSTT1* and *GSTP1* polymorphisms, however, the functional *GSTP1* substitution variant was associated with an increased breast cancer risk in Chinese women [7]. Of note, a sufficiently powered population-based case–control study from Germany recently linked the postmenopausal hormone therapy associated breast cancer risk with *GSTT1* ± and *GSTP1*_341_C > T polymorphisms. In particular, carriers of the functional *GSTT1* allele showed a statistically robust risk association for hormone use associated breast cancer compared with noncarriers and their risk to develop breast cancer increased 4% per year [9].

While the data of *GSTM1*, *GSTT1*, and *GSTP1* await confirmation or refutation from independent global case–control collections [7, 10], as of yet, sparse or no evidence for a potential contribution of *GSTA*, *GSTM2*, *GSTO*, and *GSTZ* to breast cancer risk is available. This gap needs to be addressed because due to the functional profiles of these GSTs an involvement in breast cancer risk cannot be excluded. For example, GSTA which is expressed in steroidogenic tissues is involved in steroid hormone synthesis and has high catalytic efficiency of isomerization of 3-ketosteroids which exceeds that of hydroxy steroid dehydrogenase 3 alpha more than 200-fold [11]. GSTO participates in cellular signalling and overexpression has been linked with the induction of apoptosis [12]. GSTM2 detoxifies *o*-quinones and can be up-regulated by progesterone [13, 14]. Finally GSTZ1, also known as maleylacetoacetate isomerase, plays a key role in the tyrosine catabolism [15]. This amino acid is particularly essential in enzymes of signalling processes such as receptor tyrosine kinases that are necessary for most hormone effects on cells [16].

Here we present data on nine polymorphisms at *GSTA2*, *GSTM2*, *GSTO1*, *GSTO2*, and *GSTZ1* genotyped in the German GENICA (Gene Environment Interaction and Breast Cancer in Germany) breast cancer case–control study (1021 incident breast cancer cases, 1015 age-matched controls) and show no evidence for an association with breast cancer risk.

Materials and methods

Study population

GENICA study participants of the population-based breast cancer case–control study from the Greater Bonn Region, Germany, were recruited between 08/2000 and 9/2004 as described previously [17, 18]. In brief, there are 1143 incident breast cancer cases and 1155 population controls matched in 5-year classes. Cases and controls were eligible if they were of Caucasian ethnicity, current residents of the study region, and below 80 years of age. Information on known and supposed risk factors was collected for all participants via in-person interviews. The response rate for cases was 88% and for controls 67%. DNA samples were available for 1021 cases (89%) and 1015 controls (88%). Characteristics of the study population regarding potential breast cancer risk factors include age at diagnosis (<50, ≥50 years), menopausal status (premenopausal, postmenopausal), family history of at least one-first degree relative with breast cancer (yes, no), use of oral contraceptives

Table 1 Epidemiologic baseline information and tumor characteristics of breast cancer cases and controls of the GENICA collection

		Cases *N* (%)	Controls *N* (%)	OR[a] (95% CI)
Epidemiological variables				
Age (years)	<50	225 (22.0)	226 (22.3)	
	≥50	796 (78.0)	789 (77.7)	
Menopausal status	Pre	248 (24.8)	235 (23.6)	1.00[b]
	Post	753 (75.2)	762 (76.4)	0.90 (0.65–1.24)
Family history of breast	No	845 (84.4)	914 (91.7)	1.00[b]
	Cancer			
	Yes	156 (15.6)	83 (8.3)	2.04 (1.53–2.70)
Use of oral contraceptives (years)	Never	372 (36.5)	368 (36.3)	1.00[b]
	>0 < 5	180 (17.7)	185 (18.3)	0.97 (0.74–1.28)
	5 < 10	134 (13.1)	120 (11.8)	1.11 (0.81–1.52)
	≥10	333 (32.7)	340 (33.6)	0.97 (0.76–1.25)
Use of hormone replacement therapy (years)	Never	506 (49.8)	509 (50.3)	1.00[b]
	> 0 < 10	245 (24.1)	290 (28.6)	0.86 (0.68–1.09)
	≥10	266 (26.1)	214 (21.1)	1.36 (1.05–1.76)
Body mass index (kg/m^2)	<20	88 (8.8)	70 (7.2)	1.28 (0.91–1.81)
	20 < 25	459 (45.9)	464 (46.4)	1.00[b]
	25 < 30	302 (30.1)	319 (32.0)	0.99 (0.80–1.22)
	≥30	152 (15.2)	144 (14.4)	1.08 (0.83–1.42)
Smoking	Never	586 (57.5)	555 (54.7)	1.00[b]
	Former	192 (18.8)	215 (21.2)	0.95 (0.75–1.19)
	Current	242 (23.7)	245 (24.1)	0.84 (0.66–1.06)
Tumor characteristics				
ER status	Positive	755 (77.8)		
	Negative	216 (22.2)		
PR status	Positive	678 (70.0)		
	Negative	291 (30.0)		
HER2 status	Positive	189 (27.7)		
	Negative	493 (72.3)		
Grading	G1	77 (8.2)		
	G2	567 (60.4)		
	G3	295 (31.4)		
Tumor size	T1	582 (61.9)		
	T2	289 (30.7)		
	T3	30 (3.2)		
	T4	39 (4.2)		
Histology	Ductal	634 (69.5)		
	Lobular	177 (19.4)		
	Ductolobular	101 (11.1)		
Nodal status	N0	602 (63.8)		
	≥N1	342 (36.2)		

The table includes all patients for whom genomic DNA was available

Abbreviations *CI* confidence interval, *ER* estrogen receptor, *OR* odds ratio, *PR* progesterone receptor

[a] OR conditional on age in 5-year groups adjusted for menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone replacement therapy, body mass index and smoking

[b] Reference

(never,>0–<5, 5–<10, ≥10 years), use of hormone therapy (never, >0–<10, ≥10 years), body mass index (<20, 20–<25, 25–<30, ≥30 kg/m^2) and smoking status (never, former, current) (Table 1).

Information on clinical and histo-pathological tumor characteristics was available for 1011 (99%) breast cancer cases. The dataset included estrogen receptor and status (positive, negative), progesterone receptor status (positive, negative), HER2 status (positive, negative), grade (G1, G2, G3), tumor size (T1, T2, T3, T4), histology (ductal, lobular, ductolobular), and node status (N0, N≥1) (Table 1).

The GENICA study was approved by the Ethic's Committee of the University of Bonn. All study participants gave written informed consent.

Isolation of DNA and genotyping

Genomic DNA was extracted from heparinized blood samples (Puregene™, Gentra Systems, Inc., Mineapolis, USA) as previously described [19]. Nine polymorphisms *GSTA2*_448_C > G (rs2180314), *GSTA2*_742_A > C (rs6577), *GSTM2*_-832_T > C (rs638820), *GSTO1*_-1242_G > A (rs2164624), *GSTO1*_419_A > C (rs4925), *GSTO2*_-183_A > G (rs2297235), *GSTO2*_342_A > G (rs156697), *GSTZ1*_-4378_A > G (rs1046428), and *GSTZ1*_94_G > A (rs3177427) were selected for this analysis on the basis of a known or a potential functional consequence as well as a reported allele frequency of at least 5% in Caucasians. All 2036 DNA samples were genotyped by matrix assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) as described previously using a MTP Anchor Chip™ 400/384 TF and Bruker Ultraflex I MALDI-TOF MS (Bruker Daltonics, Bremen, Germany) as well as a SpectroCHIP and Sequenom Compact MALDI-TOF MS (Sequenom, San Diego, CA, USA) [19]. For quality control, repeated analyses were performed for 20% randomly selected samples. Primers were synthesized by Metabion International AG, Martinsried, Germany, sequences are available on request.

Statistical analyses

Genotype frequencies of all polymorphisms were tested for Hardy–Weinberg equilibrium (HWE). Associations between genetic variables and breast cancer risk were analyzed by logistic regression conditional on age (5-year groups) and adjusted for six potential epidemiological breast cancer risk factors (menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index and smoking). Subgroup analysis was performed for these six epidemiological variables. Additionally, the associations between *GST* genotypes and seven clinical and histopathological tumor characteristics (estrogen receptor status, progesterone receptor status, HER2 status, grading, tumor size, histology, and node status) of breast cancer cases were analyzed by χ^2-test. All tests were two-sided. To correct for multiple testing we divided the significance level of 0.05 by the number of tested variables. In case of epidemiological variables 0.05 was divided by six and thus P-values < 0.008 were considered significant. Accordingly, for the seven tumor characteristics P-values < 0.007 were considered significant. Risk estimates were given as odds ratios (OR) and 95% confidence interval (CI). Statistical analyses were done using SAS v 9.1.3 (SAS Institute Inc., Cary, NC, USA).

Power calculation was performed using nQuery Advisor (Statistical Solutions Ltd., Cork, Ireland).

Results

Nine polymorphisms in *GSTA2*, *GSTM2*, *GSTO1*, *GSTO2*, and *GSTZ1* were genotyped in 2036 DNA samples (1015 cases, 1021 controls). Call rates were >98%, concordance of duplicates was 100% and distribution of genotype frequencies were in HWE with the exception of *GSTO1*_419_A > C frequencies in breast cancer cases. None of the analyzed polymorphisms showed an association with breast cancer risk (Table 2), with the exception of *GSTO1*_-419_AC. However, this effect was no more significant upon multiple testing. Subgroup analyses considering menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index, and smoking did not reveal any breast cancer risk associations (data not shown). No association between respective GST polymorphisms and histopathological tumor characteristics has been observed (data not shown).

Discussion

We tested nine polymorphisms in *GSTA2*, *GSTM2*, *GSTO1*, *GSTO2*, and *GSTZ1* in the German GENICA breast cancer case–control collection for their potential role in breast cancer susceptibility. The study included more than 2000 cases and controls and had an 80% power to detect a minimum OR of 1.4 for the nine polymorphisms ($\alpha = 0.05$, two-sided test). None of the polymorphisms showed an association with breast cancer risk neither in general nor in subgroup analysis with respect to menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone therapy, body mass index, and smoking. Moreover, none of the polymorphisms showed an association with histopathological tumor characteristics.

For *GSTM2*_-832_T > C, *GSTO1*_-1242_G > A, *GSTO2*_-183_A > G, and *GSTZ1*_-4378_A > G polymorphisms to our knowledge no data on this issue have been available so far.

Table 2 Genotype frequencies and risk estimates of polymorphisms located in *GSTA2, GSTM2, GSTO1, GSTO2* and *GSTZ1* in breast cancer cases and controls

Genotype	Controls *N* (%)	Cases *N* (%)	OR (95% CI)[a]
*GSTA2*_448_C > G (rs2180314)			
CC	355 (35.7)	366 (36.6)	1.00[b]
CG	477 (47.9)	482 (48.2)	0.98 (0.80–1.19)
GG	163 (16.4)	153 (15.3)	0.94 (0.72–1.23)
*GSTA2*_742_A > C (rs6577)			
AA	912 (90.4)	912 (90.2)	1.00[b]
AC	94 (9.3)	95 (9.4)	0.99 (0.73–1.35)
CC	3 (0.3)	4 (0.4)	1.41 (0.32–6.35)
*GSTM2*_-832_T > C (rs638820)			
TT	238 (24.2)	255 (25.6)	1.00[b]
TC	498 (50.7)	502 (50.4)	0.95 (0.77–1.19)
CC	246 (25.1)	239 (24.0)	0.91 (0.70–1.17)
*GSTO1*_-1242_G > A (rs2164624)			
GG	458 (45.8)	435 (43.2)	1.00[b]
GA	436 (43.6)	464 (46.1)	1.13 (0.94–1.37)
AA	105 (10.5)	107 (10.6)	1.08 (0.80–1.46)
*GSTO1*_419_A > C (rs4925)			
AA	429 (43.2)	396 (39.6)	1.00[b]
AC	456 (46.0)	509 (50.9)	1.25 (1.03–1.51)
CC	107 (10.8)	95 (9.5)	0.98 (0.72–1.34)
*GSTO2*_-183_A > G (rs2297235)			
AA	498 (49.9)	484 (48.3)	1.00[b]
AG	422 (42.3)	434 (43.3)	1.06 (0.88–1.28)
GG	77 (7.7)	85 (8.5)	1.15 (0.82–1.60)
*GSTO2*_342_A > G (rs156697)			
AA	442 (44.3)	425 (42.3)	1.00[b]
AG	453 (45.4)	456 (45.4)	1.05 (0.87–1.27)
GG	102 (10.2)	123 (12.3)	1.27 (0.94–1.70)
*GSTZ1*_-4378_A > G (rs1046428)			
AA	458 (45.8)	488 (48.7)	1.00[b]
AG	437 (43.7)	427 (42.6)	0.94 (0.78–1.13)
GG	104 (10.4)	88 (8.8)	0.78 (0.57–1.08)
*GSTZ1*_94_G > A (rs3177427)			
GG	444 (44.5)	476 (47.4)	1.00[b]
GA	445 (44.6)	436 (43.4)	0.94 (0.78–1.13)
AA	109 (10.9)	92 (9.2)	0.77 (0.57–1.06)

[a] OR conditional on age in 5-year classes, adjusted for menopausal status, family history of breast cancer, use of oral contraceptives, use of hormone replacement therapy, body mass index and smoking

[b] Reference

Abbreviations: *CI* confidence interval, *OR* odds ratio

Our study therefore provides a first data set and shows no associations with breast cancer risk.

In the case of the *GSTO1*_419_A > C polymorphism, our study also showed no association with breast cancer risk. This, however, is in contrast with two previous reports from Thailand and Denmark that reported a breast cancer risk association for the C allele. Our study differed from theirs in that we included more than thousand cases and thousand controls, whereas the study from Thailand included less than 40 and the study from Denmark less than 400 cases and controls, respectively [20, 21]. Because our study was powered to detect a putative risk association but no such risk association could be observed, we suggest that population stratification due to limited power and different ethnicities should be taken into account when interpreting the observed effects by others.

Moreover, we showed that the *GSTZ1*_94_G > A and *GSTO2*_342_A > G polymorphisms were not associated with breast cancer risk, which is in agreement with results reported by Smith et al. [22] for *GSTZ1* in a study from Australia and Marahatta et al. [20] who investigated 30 cases and 98 controls from Thailand. This also refers to the closely linked *GSTA2*_448_C > G, *GSTA2*_742_A > C polymorphisms, of which a recently published study from Portugal showed no breast cancer risk association based on 291 cases and 547 controls [23].

In summary, we conclude that polymorphisms *GSTA2*_448_C > G, *GSTA2*_742_A > C, *GSTM2*_-832_T > C, *GSTO1*_419_A > C, *GSTO1*_-1242_G > A, *GSTO2*_-183_A > G, *GSTO2*_342_A > G, *GSTZ1*_94_G > A, and *GSTZ1*_-4378_A > G are not associated with breast cancer risk and it is therefore unlikely that glutathione S-transferases GSTA2, GSTM2, GSTO1, GSTO2, and GSTZ1 participate in breast cancer susceptibility.

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